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REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application. Applicants request reconsideration of the subject application based on the instant amendments to the claims and the following remarks.

Claims 28-34 are pending in the application. Claims 28-31, 33 and 34 have been amended. No new matter has been introduced by the instant amendments. Original claims 1-11, 13-18 had been withdrawn due to restriction requirement. Claims 12, 19-27 had been canceled. Applicants reserve the right to pursue the subject matter cancelled/withdrawn by this or a prior action in this or a subsequent continuation application.

Claims 28-34 stand rejected under 35 U.S.C. §112, second paragraph as failing to set forth the subject matter which applicants regard as their invention.

Claims 28, 30-32 stand rejected under 35 U.S.C. §112, first paragraph because the specification does not enable any person skilled in the art to make/use the invention commensurate in the scope with these claims.

Claims 28-30 stand rejected under 35 U.S.C. §103(a) as obvious over the Jenuwein et al (US PAT 6555329 B2) in view of Jenuwein et al (US PAT 6689583)

Claims 31-34 stand rejected under 35 U.S.C. §103(a) as obvious over Kouzarides et al. (WO 02/090578) in view of Jenuwein et al (US PAT 6689583)

Rejection under 35 U.S.C. §112, second paragraph

Claims 28-34 stand rejected under 35 U.S.C. §112, second paragraph as being confusing and indefinite since it is unclear whether steps (a) and (b) are separate reactions or sequential steps that are performed on the same reaction. In order to clarify that steps (a) and (b) are separate reactions, the applicants amended claims 28-31, 33 and 34 by inserting "wherein step (a) and step (b) are conducted separately" after step (b).

Rejection under 35 U.S.C. §112, first paragraph

Claims 28, 30-32 stand rejected under 35 U.S.C. §112, first paragraph since the specification does not reasonably provide enablement for methods of identifying any agent to prevent breast cancer. The Office Action further stated that the specification fails to describe how histone methyl transferase inhibitor will prevent breast cancer.

The rejection is respectfully traversed. The amended claims 28, 30 and 31 are directed to "A method of screening a candidate for the preventive or therapeutic agent for cancer in which expression of histone methyltransferase is increased, ...". Support for this amendment are found at page 27, line 34 to page 28, line 6, and page 28, line 12. The claimed screening method provides compounds which are a candidate for preventive agent for breast cancers which relate to increased HMTase expression.

Thus, the Examiner's concerns with regard to the preventive agent for breast cancer have been alleviated by the present amendment. Withdrawal of the rejection under § 112 is earnestly solicited.

Rejection under 35 U.S.C. §103(a)

Claims 28-30 stand rejected under 35 U.S.C. §103(a) as obvious over Jenuwein et al (US PAT 6555329 B2, hereinafter D1) in view of Jenuwein et al (US PAT 6689583, hereinafter D2). The office action stated as follows:

> Jenuwein et al (US PAT 6555329B2, page 13) teach SUV39H1 expresses in tumor cell and involves in tumor growth and suggested that HMTase inhibitor will be useful in cancer therapy (US PAT 6555329B2, page 13)

The office action further stated:

> Jenuwein et al. (PAT 6689583) suggest the modulation the HMTase of SEQ ID NO: 4 which has 100 % sequence identity with the SEQ ID NO: 1 of the present application for controlling tumor growth (abstract). Furthermore, both HMTases (US PAT 6555329B2) and (Pat 6689538) perform the same reaction whether they have or have not have exact same structure. Therefore one

knowledgeable in prior art will use Jenuwein et al's (US PAT 6689583) histone methyl transferase protein of SEQ ID NO: 4. (which has 100 % sequence identity with the SEQ ID NO: 1 of the present application) upon the teaching and suggestion of Jenuwein et al (US PAT 6555329 B2) in the method of screening modulators of histone methyl transferase and suggestion to use them as therapeutic agent for cancer and apoptosis inducer (page 14 paragraph 20-45) as taught by Jenuwein et al (US PAT 6555329 B2).

The rejection is respectfully traversed. There are a variety of cancers which are caused by different mechanisms. No cancer therapy can universally treat all cancers at present. In fact, D1 discloses only mouse embryonic fibroblasts (PMEFs), fetal liver and bone marrow cells and in spermatogenola, in which absence of Suv39h HMTase activities triggers genomic instabilities (column 6, lines18-21). D1 merely stated that SUV39H1 inhibitor is useful in cancer therapy. That, however, does not necessarily mean SUV39H1 inhibitor is useful in breast cancer therapy. All the relevant working examples in D1 employed PMEFs, which is different from breast cancer cells. D1 neither disclosed nor suggested the relationship between breast cancer and SUV39H1. Similarly, D2 does not disclose any association of SUV39H1 with breast cancer.

On the other hand, the specification of the present application taught and specifically substantiated the methods of screening a candidate for preventive or therapeutic agent for breast cancer in which expression of histone methytransferase is increased. For example, in EXAMPLE 1 of the present specification, it was substantiated that SUV39H1 is specifically expressed in the breast cancer tissue (Patient No.6: see TABLE 2). In EXAMPLE 2, it was substantiated that SUV39H1 is not only expressed specifically in the breast cancer tissue, but is engaged in cancer cell growth.

It is the inventors of the present application that found and substantiated, for the first time, that SUV39H1 is specifically related to breast cancer.

As to claim 29, the amended claim 29 is directed to a method of screening an apoptosis inducer for a cancer cell line. Support for the amendment can be found at page 28 lines 2-10 of the specification.

D1 stated that Suv39-mediated defects in male meiosis induce pronounced apoptosis of stage V-VI spermatocytes during the transition from mid to late pachytene (column 7, lines 19-22, and Example 12). This statement rather shows Suv 39h is associated with melosis in germ cell, not with mitosis in somatic cell including cancer cell line.

Therefore, there is neither suggestion nor motivation for combining D1 with D2 in these references. It is not believed obvious for a skilled person to use modulators of HMTase obtainable by the assay method in D2 as apoptosis inducer as taught by D1.

Any rejection of a claim for obviousness over a combination of prior art references must establish that (1) the combination produces the claimed invention and (2) the prior art combines a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention (In re Vaek, 947 F.2d 488; 20 USPQ2d 1438-Fed.Cir.1991). In addition, the Examiner's prima facie case must include a finding that one of ordinary skill in the art at the time the invention was made would have reasonably expected the claimed invention to work (In re O'Farrell, 853 F.2d 894, 903-904; USPQ2d 1529, 1531-Fed. Cir. 1988). In the present office action, the Examiner has not established a prima facie case of obviousness.

Thus, for at least these reasons, claims 28 – 30 are patentable over D1 and D2.

Claims 31-34 stand rejected under 35 U.S.C. §103(a) as obvious over Kouzarides et al. (WO 02/090578, hereinafter D3) in view of Jenuwein et al (US PAT 6689583, D2). The office action stated as follows:

> it is immaterial what is the purpose the method of MALDI mass spectrometry detect the similar substances (i.e. methylated and unmethylated substances to find out the extend of methylation) and it is obvious one skilled in prior art to use the same method of MALDI mass spectrometry that used by Kouzarides et al and Jenuwein et al's to screen modulators of said histone methyl transferase.

The rejection is respectfully traversed. The amended claims 31 and 34 are directed to method of screening comprising steps of (c) measuring the molecular weight of the purified reaction products, by mass spectrometry, obtained in steps (a) and (b), and (d) comparing the results measured in step (c) using, as an indicator, changes in molecular weight accompanied by methylation. Support for the amendment can be found at page 30 lines 2-12 of the specification. In these screening method, the methylation reaction products obtained in steps (a) and (b) are purified and the molecular weight of the purified products are measured by mass spectrometry. Here the HMTase modulator is screened as a result of comparison of molecular weight of reaction product of step (a) with the molecular weight of the reaction product of step (b), which difference is accompanied by methylation.

In D3, mass spectrometry was used for identifying a set of proteins binding to unmethylated H3 peptides, resulting in identification of known components of the NuRD complex (see, e.g., line 23 in page 48 to line 7 in page 49, line 28 in page 53 to line 14 in page 54 of D3). There is no disclosure of comparison by MALDI mass spectrometry in D3.

In addition, Jenuwein et al (US 6,689,583 B1, D2) used mass spectrometry to identify new Suv39h substrate, i.e., "equivalent to or mimicking the naturally occurring substrate, e.g., biochemically purified histone H3..." (column 12, lines 17-30).

Neither D2 nor D3 suggested or taught changes of the molecular weight of the reaction product accompanied by methylation are measured by mass spectrometry. Thus, it is believed that a skilled person could not have been motivated to combine D2 and D3, to utilize the mass spectrometry for the screening method as disclosed in D2.

Thus, for at least these reasons, claims 31 and 34 are patentable over D2 and D3.

The subject matter recited in claim 33 is not the screening method using mass spectrometry as described in D2 and D3. Withdrawal of rejection under 35 U.S.C. §103(a) is solicited.

In view of the foregoing, applicants respectfully request reconsideration, withdrawal of all grounds of rejection and objection, and allowance of claims 28 to 34 in due course.

Respectfully submitted,

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